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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,326	07/13/2005	Alan Wellington Faull	06275-461US1 100929-1P US	7821

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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,326	FAULL ET AL.	
	Examiner	Art Unit	
	Janet L. Coppins	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8, 11-13 and 15-20 are pending in the instant application.

Priority

2. The instant application is a 371 of PCT/GB04/00096, filed January 13, 2004, which has benefit of foreign priority to Sweden 03000924, filed January 15, 2003.

Lack of Unity

3. Applicant's election of Group I, drawn to compounds, compositions, processes and methods of Formula I, wherein A is phenyl, CR3R4 do not form a ring, and R5 does not contain a Het ring, in the reply filed on May 7, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

4. Accordingly, Groups II-LVI, i.e. claims 1-8, 11-13 and 15-20 wherein A is other than phenyl, or CR3R4 do form a ring, or R5 does contain a Het ring, are currently withdrawn from further consideration as being drawn to nonelected inventions.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11, 15 and 20 are rejected under 35 U.S.C. 112, first paragraph, as not being fully enabled. The specification, while being enabling for treating certain diseases that benefit from the inhibition of IKK-2, does not reasonably provide enablement for treating all of the diseases/disorders encompassed by the language of the aforementioned claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Regarding claims 15, while various diseases/disorders may be listed in the specification, the claims are not enabled for *all* disorders responsive to the "inhibition of IKK-2 activity," since there is no indication as to the full range of disorders that could be treated using the instant claimed method. Regarding claim 11, the claims are not enabled for *any* and *all* "inflammatory diseases," and are likewise not enabled for treating "cancer" (claim 20).

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The specification, while being enabling for compounds according to formula (I) for treating certain diseases that respond to the inhibition of IKK-2, does not reasonably provide enablement for treating all of the diseases encompassed by the above claims.

Applicants are claiming a method of treating any condition in which the inhibition of IKK-2 is beneficial (claim 15), and methods of treating or preventing many unrelated diseases, (those encompassed by "inflammatory diseases") that are not enabled, and cancer (claim 20).

The nature of the invention

The nature of the invention is methods of treating inflammatory diseases, or diseases involving IKK-2 and the NF-κB pathway, comprising administering a compound to a patient in need thereof. The language of claims 11 and 15 encompasses *any* or *all* inflammatory disorders/diseases as well as any disease capable of being treated via the inhibition of IKK-2. Claim 20 encompasses any and all forms of cancer or cancerous tumors.

The state of the prior art

The state of the prior art is that IKK-2 is a protein kinase (specifically a serine/threonine kinase) and is involved in the regulation of NF-κB, which plays an important role in coordinating the inflammatory response. The NF-κB nuclear factor is known to be implicated in diseases/disorders such as inflammation, allergy, rheumatoid arthritis, GVHD, rhinitis, asthma, and in certain proliferative diseases such as cancer.

Furthermore, "a method for the treatment or prophylaxis of inflammatory diseases" encompasses many diseases, including, for example inflammatory arthritis including rheumatoid arthritis, osteoarthritis, spondylitis, Reiters syndrome, psoriatic arthritis, lupus and bone resorptive disease; multiple sclerosis, inflammatory bowel disease including Crohn's disease; asthma, chronic obstructive pulmonary disease, emphysema, rhinitis, myasthenia gravis, Graves' disease, allograft rejection, psoriasis, dermatitis, allergic disorders, immune complex diseases,

cachexia, ARDS, toxic shock, heart failure, myocardial infarcts, atherosclerosis, reperfusion injury, diabetes, hyperglycemia, hyperinsulinemia, dyslipidemia, obesity, polycystic ovarian disease, hypertension, cardiovascular disease, as well as AIDS and cancer, for which there is no known cure, and certainly no prevention. Likewise, "a method of treating... a disease or condition in which inhibition of IKK-2 activity is beneficial" encompasses any and all forms of the aforementioned diseases, as well as cancer, for which there is also no know cure.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of the inhibition of IKK-2 activity on said diseases, whether the inhibition of IKK-2 would affect the possible treatment of each disease listed or encompassed. The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. In the absence of a showing of correlation between all the diseases claimed as capable of being treated by the compound of claim 1 and the inhibition of IKK-2, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1.

As to treating or preventing "cancer" by use of compounds, of formula (I), the examiner was not able to locate prospective clinical studies in the art demonstrating blanket "prevention"

of any and all types of cancer, let alone treatment, so there were no benchmarks against which to compare the efficacy of the claimed chemical compounds of formula (I) for the absolute treatment of all cancers, had the Specification done so. In light of the highly unpredictable nature of this art, the Specification failed to disclose facts that would enable the skilled artisan to use the compounds of formulae (I) to prevent or treat cancer without undue experimentation.

The amount of direction or guidance present and

the presence or absence of working examples

The specification has enabled only the compounds according to formula (I) that selectively inhibit IKK-2. Treatment of the claimed distinct disorders/diseases are normally disease or symptom oriented, thus are highly individualized, i.e. treating the symptoms of asthma (sudden recurring attacks of labored breathing, chest constriction, and coughing) would not employ the same methods as treating the symptoms of rheumatoid arthritis (stiffness and joint pain). The efficacy of an individual compound against a specific disease or symptom needs to be specifically and individually supported by factual evidence. Such evidence has not been described or supported by the specification.

The direction present in the instant specification is that the compounds of claim 1 can inhibit the activity of IKK-2 which helps regulate NF-κB. There are no working examples for any diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease besides the *in vitro* inhibition of IKK-1 and IKK-2.

The specification only discusses an *in vitro* inhibition assay on pages 46-48, demonstrating concentrations of the claimed compounds of formula (1) needed to suppress 50%

suppression of cell proliferation (IC_{50} values), please see the Specification, Results on page 48.

The breadth of the claims

Applicants are claiming methods of treating a broad number of diseases that are unrelated. The allegation that the diseases claimed by the Applicants are all connected to the inflammatory response or implicate the IKK-2 enzyme is insufficient support that the claimed compounds have specific efficacy in current available form for treating all of the diseases/disorders encompassed by the language of the claims.

The text of claim 20 does not specify or enumerate those many types of cancer that would fall within its scope. The applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." In view of this rule, claim 20 may be reasonably interpreted to encompass all forms of cancer or cancerous tumors, as neither claim 20 itself nor the Specification expressly defines a closed set of illnesses defined as "cancer." Specifically, claim 20 itself states only that the compounds are for treating cancer and therefore claim 20 encompasses an open-ended set of types of cancer.. The scope of claim 20 reasonably encompasses such a broad spectrum of types of cancer that it is unreasonable to believe, on its face, that a particular chemical compound could be used for "treating or reducing the risk of" of so many different types of cancer, in the absence of supporting scientific data or references in the disclosure to the contrary. Due to the unpredictable nature of cancer and the fact that over 3,000 different cancers exist, the various types of cancers have different causative agents, involve different cellular mechanisms, and differ in treatment protocol, thus no single compound exists presently that is known to treat *all* cancers as a blanket therapeutic. Furthermore, the Merck® manual currently has many cancer

treating agents (over 12,000 compounds), yet they are only known to treat one cancer each.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art without direction, would be unable to treat each and every disease/condition encompassed by claims 11 and 15 as well as cancer of claim 20, using the instant claimed compounds. One of skill in the art would need to determine which diseases/disorders would be benefited by inhibiting the IKK-2 enzyme and would furthermore then have to determine whether the claimed compounds would provide treatment of all of the disorders and conditions encompassed by claims 11 and 15. Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine whether the claimed compounds not only inhibit the activity of an enzyme, but also treat disorders of real-world relevance.

When considering the claim of treating or preventing the broad array of types of cancer of claim 20 using compounds of formula (I), in the context of the state of the art at the time of the invention, the absence of direction of working examples in the Specification, and the unpredictability of using the claimed invention for treating cancer, one skilled in the art would require an undue quantity of experimentation even to select which of the many compounds of formula (I) would be useful to treat or prevent cancer, or to select those persons (presumably both with or without cancer) who would benefit by administration of the claimed invention, and the skilled artisan would have little assurance of success.

One skilled in the art would require an undue quantity of experimentation to make or use the invention for inhibiting all of the claimed types of cancer or cancerous tumors; however, it

would not require an undue quantity of experimentation for the skilled artisan to use the invention for "inhibiting the growth of" certain types of cancer tumors, with a reasonable likelihood of success. The Examiner recommends limiting the scope of claim 20 to encompass "a method of inhibiting the growth of a cancerous tumor in patient, wherein the cancer is selected from the group consisting of" and then insert the above-mentioned cancers or tumor cell lines, as enabled by the art of record.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Regarding claim 15, the Examiner suggests claiming the possible diseases and conditions that are treated, rather than claiming the mechanism, which is speculative, and recommends the

following language, "A method of inhibiting IKK-2, for treating _____ , comprising administering to a patient in need thereof an effective amount of a compound of a compound of formula (I)...."

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-8, 11-13 and 15-20 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-11, 21, 26 and 33 of copending Application No. 09/868,884. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: the claims of the '884 Application are drawn to phenyl-thiophene-

carboxamides according to formula (1) that are also useful as IKK-2 inhibitors, and their pharmaceutical compositions, their processes of preparation, and their methods of use. The compounds of the '884 Application, wherein "R1" is phenyl substituted by $-(CH_2)R11$ wherein "R11" is NR21R22 (R21 and R22 are both either hydrogen or optionally substituted alkyl), and "R2" is hydrogen; are the same as those instantly claimed wherein R^1 is hydrogen, R^2 is hydrogen, R^3 and R^4 are hydrogen, X is NR^6 wherein R^6 is hydrogen or alkyl, and R^5 is hydrogen or optionally substituted alkyl.

Conclusion

10. In conclusion, claims 1-8, 11-13 and 15-20 are pending and all claims stand rejected.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Coppins
August 4, 2007

for Joseph K. McKane
SPE, Art Unit 1626